Research Suggests Therapy Against Side Effects of Smallpox Vaccine

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DENVER — Smallpox is considered a potential terrorist weapon, but millions of people in the United States are currently advised not to get a vaccine to the disease because they are susceptible to developing a severe adverse reaction. Researchers at National Jewish Medical and Research Center report in the March issue of *Immunity* that a deficiency in the innate immune response may pre-dispose patients with atopic dermatitis, or eczema, to developing the skin condition eczema vaccinatum after vaccination. The findings suggest potential therapeutic targets, which may reduce the risk of this devastating side effect.

"I believe these findings could have a significant impact on our ability to vaccinate individuals with eczema and better protect them against potential bio-terrorist attacks involving smallpox," said Michael Howell, PhD, first author of the report and Instructor of Pediatrics at National Jewish Medical and Research Center. "We identify potential therapies, which should be further tested to determine if they can effectively and safely protect susceptible patients against eczema vaccinatum."

Eczema vaccinatum occurs when the vaccinia virus, which is currently used for the smallpox vaccine, replicates uncontrollably and circulates through the entire body. Eczema vaccinatum kills 1 to 6 percent of those affected. Up to 30 percent of children younger than 2 years of age with the disease die. It is also possible that atopic dermatitis patients can develop eczema vaccinatum even if they don't get the vaccine, but come into close personal contact with people who recently received the vaccine.

Approximately 17 percent of children in the United States are diagnosed with atopic dermatitis, suggesting that close to 50 million people in the United States face an increased risk of eczema vaccinatum following the smallpox vaccine. The U.S. Centers for Disease Control currently recommends that individuals with atopic dermatitis, and those who come into close contact with them, do not receive the live vaccine due to potential adverse reactions. This accounts for approximately 50 percent of the population in the United States. In case of an actual smallpox outbreak, they would likely receive the vaccine and face the increased risk of developing eczema vaccinatum.

The National Jewish research team, led by Donald Leung, MD, PhD, Edelstein Family Chair of Pediatric Allergy-Immunology, had previously reported that atopic dermatitis patients have lower levels of disease-fighting antimicrobial peptides in their skin than people without the disease. They also reported that one particular antimicrobial peptide, called LL-37, could kill vaccinia virus when it is grown in cell culture.

In their current report, the researchers found that lower levels of LL-37 in the skin of patients with atopic dermatitis did indeed allow the uncontrolled growth of vaccinia virus. Skin cells from atopic dermatitis patients failed to increase LL-37 production in response to the vaccinia virus infection, while skin cells from healthy controls and patients with the skin disease psoriasis samples did ramp up LL-37 production. When the researchers added LL-37 to the infected atopic dermatitis skin cells, vaccinia virus growth slowed significantly.

"It is becoming increasingly clear how important antimicrobial peptides are in immune defense," said Dr. Leung. "They are part of the fast-acting, innate immune response. Because atopic dermatitis patients fail to mount a vigorous innate response with antimicrobial peptides, vaccinia virus infection gets well established and the slower adaptive immune response cannot eradicate it."

Atopic dermatitis patients have high levels of signaling molecules interleukin-4 (IL-4) and interleukin-13 (IL-13) in their skin. The researchers found that IL-4 and IL-13 inhibited the production of LL-37 in atopic dermatitis patients. When they added antibodies to neutralize the two interleukins, levels of LL-37 rose in atopic dermatitis patients, and the vaccinia virus infection was controlled.

"Antibodies or other drugs that neutralize IL-4 and IL-13 are currently being developed," said Dr. Howell. "We think they should be evaluated as potential therapies that could be given at the same time as the smallpox vaccine as protection against potentially fatal side effects."

The research was funded by the National Institute of Allergy and Infectious Diseases and is part of the ongoing work of the Atopic Dermatitis and Vaccinia Network.

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